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RESEARCH ARTICLE

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Patient characteristics associated with conversion from negative to positive severe acute respiratory syndrome coronavirus-2 polymerase chain reaction test results: Implications for clinical false-negativity from a single-center: A case-control study

Vidya L. Atluri[1,2] | Randy M. Stalter[3] | Sarah A. McGuffin[1] | Luke Johnson[4] | Bailey Healy[4] | Hailey A. Benesch[4] | Kristine Lan[1] | Paula Marsland[4] | Paul Pottinger[1] | Rena C. Patel[5]

[1]Department of Medicine, University of Washington, Seattle, Washington, USA

[2]Department of Medicine, Veterans Affairs Central California Healthcare System, Fresno, California, USA

[3]Department of Epidemiology, University of Washington, Seattle, Washington, USA

[4]School of Medicine, University of Washington, Seattle, Washington, USA

[5]Departments of Medicine and Global Health, University of Washington, Seattle, Washington, USA

Correspondence

Vidya L. Atluri, Veterans Affairs Central California Healthcare System, 2615 E Clinton Ave, Fresno, CA 98195, USA.
Email: vidya.atluri@va.gov

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Abstract

Background: Accurate diagnosis of coronavirus disease 2019 is essential to limiting transmission within healthcare settings. The aim of this study was to identify patient demographic and clinical characteristics that could impact the clinical sensitivity of the nasopharyngeal severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) reverse transcription polymerase chain reaction (RT-PCR) test.

Methods: We conducted a retrospective, matched case-control study of patients who underwent repeated nasopharyngeal SARS-CoV2 RT-PCR testing at a tertiary care academic medical center between March 1 and July 23, 2020. The primary endpoint was conversion from negative to positive PCR status within 14 days. We conducted conditional logistic regression modeling to assess the associations between demographic and clinical features and conversion to test positivity.

Results: Of 51,116 patients with conclusive SARS-CoV2 nasopharyngeal RT-PCR results, 97 patients converted from negative to positive within 14 days. We matched those patients 1:2 to 194 controls by initial test date. In multivariate analysis, clinical suspicion for a respiratory infection (adjusted odds ratio [aOR] 20.9, 95% confidence interval [CI]: 3.1–141.2) and lack of pulmonary imaging (aOR 4.7, 95% CI: 1.03–21.8) were associated with conversion, while a lower burden of comorbidities trended toward an increased odds of conversion (aOR 2.2, 95% CI: 0.9–5.3).

Conclusions: Symptoms consistent with a respiratory infection, especially in relatively healthy individuals, should raise concerns about a clinical false-negative result. We have identified several characteristics that should be considered when creating institutional infection prevention guidelines in the absence of more definitive data and should be included in future studies.

KEYWORDS

clinical sensitivity, COVID-19, SARS-CoV2 RT-PCR

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1 | INTRODUCTION

Accurate diagnosis of severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) infections remains critical for control of the pandemic and limiting exposures in healthcare settings. Analytical sensitivity of the SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) is high.[1] However, reported clinical sensitivity has ranged from 58% to 99%.[2–4] This wide range has been attributed to sample site, suboptimal sampling, timing of testing, and/or low viral loads.[2,5–8]

Some studies have evaluated the frequency of conversion from an initial negative to a later positive RT-PCR in patients who were repeatedly tested for SARS-CoV2.[9–11] These studies suggested that the timing of presentation, viral load, or test indication can be associated with conversion. However, none have systematically determined the demographic and clinical features associated with conversion in both outpatient and inpatient settings. Identification of those features could prompt providers and health systems to have higher thresholds for discontinuing precautions on patients at risk for conversion from negative to positive PCR result. Here, we conducted a matched case-control study to explore potential patient characteristics that could be associated with conversion from negative to positive nasopharyngeal (NP) SARS-CoV2 RT-PCR test result within 14 days of the initial negative test result.

2 | METHODS

2.1 | Study setting, site, and population

We conducted a matched case-control study of patients with electronic medical record (EMR) data collected from March 1 through July 23, 2020, from the University of Washington Medicine (UWM) system. This system includes multiple hospitals, outpatient settings, emergency departments, drive-through test sites, and mass testing of nursing homes in collaboration with the local and state public health departments.[12] This study was approved by the Human Subjects Division.

2.2 | Study design

For our primary analysis reported earlier, we included all persons who had their sex recorded in the EMR and had a conclusive diagnostic SARS-CoV2 RT-PCR test result between March 1, 2020 to June 23, 2020.[13] That study examined the associations between sex and coronavirus disease 2019 (COVID-19) outcomes. For this study, we selected a subset of those patients as cases and controls.

The study cases included all patients with NP SARS-CoV2 RT-PCR repeated within 14 days where the first result was negative (initial test), and the second result was positive (repeat test). For patients with more than two NP SARS-CoV2 RT-PCR results within 14 days, we selected the first positive result as the repeat test and the latest negative result before that as the initial test, with all other tests excluded.

Potential controls included all individuals who had two negative SARS-CoV2 RT-PCR tests within 14 days and did not test positive during the observation period. For each of the cases, we randomly selected two of the potential controls with the same initial test date as the case (1:2 matching ratio). We included patients for whom the initial NP SARS-CoV2 RT-PCR result at UWM was negative, even when they had prior positive results from non-NP samples or from outside of our system.

The testing platforms included Panther Fusion SARS-CoV-2 assay (Hologic, Marlborough, MA, target genes two conserved regions of ORF1ab), Roche RT-PCR (Basel, Switzerland, target E gene), and DiaSorin (Saluggia, Italy, targets ORF1ab and S gene) as well as a UW laboratory-developed assay.[14]

2.3 | Data collection and management

After selection of cases and controls, we used Research Electronic Data Capture (REDCap) for data collection during the chart review process.[15,16] We extracted patient demographics (age, sex, and race/ethnicity), comorbidities, insurance status, and zip code from the EMR. A team of two physicians and four medical students conducted manual chart review to collect data that could not be extracted. These team members were blinded to individuals' case/control status and were randomly assigned charts to review. Before starting review, all members of the team reviewed charts for the same five patients to standardize variable definition and data collection. The team members met to discuss and reconcile any discrepancies. We reviewed the demographics section, primary care notes, admission notes, and social worker notes to collect information regarding the encounter status, patient's housing status, employment status, and history of exposure to SARS-CoV2. We reviewed vital signs, admission notes, and progress notes in the 48 h surrounding the test date to ascertain the symptoms and clinical reasoning for conducting the SARS-CoV2 test. Some patients had frequent, repeated imaging, and others none. For patients with imaging, only exams performed on the date of the test were included.

2.4 | Variable definitions—exposures

2.4.1 | Patient characteristics and demographics

We defined working on-site as any job that required the patients to leave their home in the prior 2 weeks. We defined confirmed COVID-19 contacts as people reported by the patient to have tested positive for SARS-CoV2 and suspected COVID-19 contacts as people reported by the patient to have symptoms consistent with COVID-19 without a confirmed test result. We defined direct contact as in-person contact with an individual, with or without appropriate personal protective equipment. We defined indirect

contact as shared workspace or residential space with individuals with confirmed or suspected COVID-19. We classified patients of the Seattle Cancer Care Alliance, a facility within UWM which primarily cares for patients with cancer, as cancer center associated patients. Due to the highly immunosuppressed nature of their specific patient population, the cancer center's SARS-CoV2 RT-PCR testing guidelines were independent from the other centers in this study.

2.4.2 | Symptoms

We defined number of days of symptoms as days between the date reported for symptom onset by the patient as documented in care notes and the date of the test. If there were conflicting dates in various notes, we chose the most consistently reported date.

We defined days between tests as the number of days between the initial and repeat test.

We defined upper respiratory tract symptoms as rhinorrhea, nasal congestion, or sore throat. We defined lower respiratory tract symptoms as chest pain, new or worsening cough, or shortness of breath. We defined systemic symptoms as fever, chills, fatigue, weakness, dizziness, myalgias, or arthralgias. We defined gastrointestinal symptoms as anorexia, loss of appetite, diarrhea, nausea, vomiting, or abdominal pain. We defined neurological symptoms defined as anosmia, ageusia, headache, or altered mental status.

If notes documenting the symptoms of patients were available, then we labeled any symptoms not mentioned in the note as absent in the patient at the time of the test. If there were no notes referring to the events surrounding the date of the test, we label the information regarding symptoms as missing or unknown.

2.4.3 | Imaging

We combined results from x-rays and computed tomography scans to characterize pulmonary imaging. We defined abnormal lung findings as consolidations, atelectasis, edema, effusions, or pulmonary embolism. We defined consolidations on imaging as any reference to consolidations, opacities, or "atelectasis versus pneumonia" in the radiology report.

2.4.4 | Variable definitions—outcomes

The primary outcome was conversion from a negative to positive NP PCR test result within 14 days of the initial negative NP PCR test date.

2.4.5 | Variable definitions—covariates

We defined age as the age at the time of the first test conducted within UWM. We collected sex from the EMR. We derived a binary socioeconomic status (SES) variable using the type of health insurance and Area Deprivation Index based on the 5- or 9-digit (where available) zip code recorded in the address field of the EMR.[13,17,18] We calculated the Charlson Comorbidity Index (CCI) with International Classification of Diseases (ICD) 9 and ICD 10 diagnostic codes recorded in the EMR.[19]

2.4.6 | Missing data

We used multiple imputations by chained equations (MICE) to account for missing race/ethnicity and SES variables from the larger study on sex associations with COVID-19 outcomes. We used imputation models using polytomatous regression to predict race/ethnicity and SES. MICE models included sex, severe COVID-19 status, age, race/ethnicity, SES, comorbidities, other sociodemographic and clinical characteristics (including testing facility, testing calendar month, marital status, and language preference) from the larger data set as predictors. Twenty imputations were generated.

2.5 | Statistical analysis

We present frequencies and percentages for categorical variables and median and interquartile range (IQR) for continuous variables. We used conditional logistic regression to assess for differences in odds of conversion from a negative to positive test result related to demographic and clinical characteristics. We report unadjusted and adjusted odds ratios (OR and aOR) with 95% confidence intervals (CI). In univariate analyses, we identified all variables associated with a difference in odds of conversion with a $p < 0.2$. We tested for collinearity between each of those variables. We then constructed a multivariable model that included variables with $p < 0.2$ in univariate analyses and entered sex, age, and SES based on a priori hypothesized relationships to identify the variables most associated with conversion to a positive result. If variables were collinear, we only included one of the variables. Since the multivariate model was intended to assist infection preventionists in determining which patients with negative test results should remain in isolation pending further testing, we included only characteristics known at the time of the initial test in the model. We then conducted a secondary sensitivity analysis in which removed asymptomatic cases and their matched controls. Where models included imputed race/ethnicity and SES variables, we calculated model parameter estimates separately for each of the 20 imputed datasets and averaged; standard errors were pooled using Rubin's Rules to obtain 95% CI and *p*-values.

All data analyses were conducted using R version 4.0.2 (R Core Team, Vienna, Austria).

3 | RESULTS

From March 2, 2020 to July 23, 2020, 51,116 patients had a conclusive NP SARS-CoV2 RT-PCR result (Figure 1). Of those, 4911 (9.6%) had multiple NP SARS-CoV2 RT-PCR tests done within

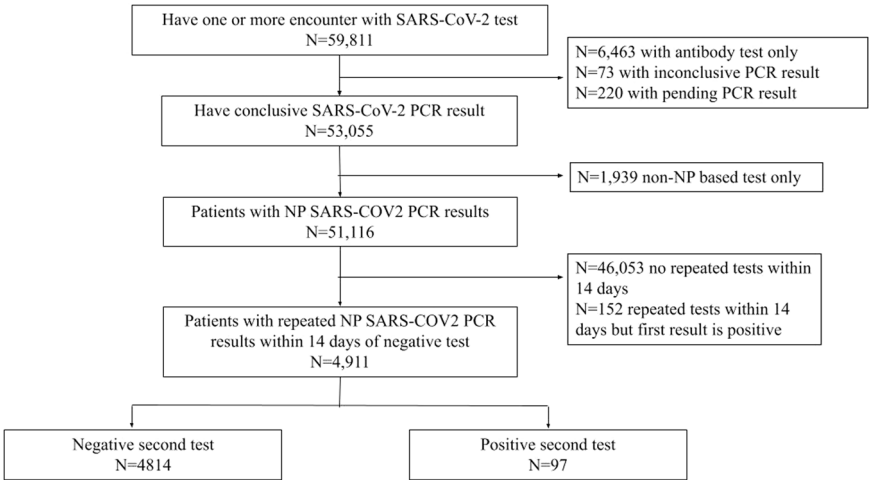

FIGURE 1 Flow diagram of patient inclusion

14 days of a negative result. Ninety-seven (2.0%) individuals converted from a negative to a positive result within those 14 days. These were matched with 194 controls by initial test date.

3.1 | Patient demographic characteristics

Patient characteristics are described in Table 1. 51.5% of cases and 57.7% of controls were male (OR = 0.8, 95% CI: 0.5–1.3). Only 38.1% of cases were non-Latinx white while the majority of controls (57.7%) were non-Latinx white. Cases identified as Latinx patients more commonly than controls (14.4% vs. 7.7%; OR 2.4, 95% CI: 1.0–5.6). Cases trended toward higher SES (55.7% vs. 47.9%; OR = 0.7, 95% CI: 0.5–1.2) and having fewer comorbidities (no CCI were 39.2% vs. 17.5% in cases vs. controls; OR = 3.7, 95% CI: 2.1–6.4). Of note, cases were less likely to have a diagnosis of systemic lupus erythematosus (10.3% vs. 21.1%). Cases were also more likely to live in a skilled nursing or assisted living facility (21.6% vs. 10.3%; OR = 2.9, 95% CI: 1.4–5.9) or have to work on-site (18.6% vs. 8.8%; OR = 2.7, CI: 1.3–5.8). Both groups were equally likely to be homeless (approximately 11.3%). Cases were much more likely to report an exposure to individuals with laboratory confirmed or suspected SARS-CoV2 infection (confirmed 28.9% vs. 6.2%, OR = 5.3, 95% CI: 1.7–16.7; suspected 12.4% vs. 1%, OR = 15.6, 95% CI: 2.8–88.2 cases vs. controls). Cases were less likely to be cancer center-associated patients (7.2% vs. 29.9%; 0.2, 95% CI: 0.1–0.5).

3.2 | Symptom evolution

Testing in all patients was typically done between 0 and 9 days after the start of symptoms (Table 2). There was a median of 6 (IQR 4–9) days between the initial and repeat test. At the time of the initial test, cases and controls were equally likely to report respiratory (26.8% vs. 29.9%, cases vs. controls; OR = 1.2, 95% CI: 0.7–2.3) or systemic symptoms (16.5% vs. 17.5%, cases vs. controls, OR = 1.2; 95% CI: 0.6–2.5). Cases less frequently reported gastrointestinal symptoms (3.1% vs. 11.9%; OR = 0.3, 95% CI: 0.1–1.1). Cases less commonly underwent asymptomatic screening (12.4% vs. 29.9%; OR = 0.7, 95% CI: 0.4–1.3). Cases had pulmonary imaging on the day of the test less commonly (17.5% vs. 36.1%; OR = 2.9, 95% CI: 1.1–7.8). Abnormalities in their lung imaging were noted in only 12.4% of cases, but 23.7% of controls (OR = 1.2, 95% CI: 0.4–3.7). However, cases were more likely to have a new/worsening cough (14.4% vs. 3.6%; OR = 7, 95% CI: 2.4–20.5) or new fever (19.6% vs. 7.7%; OR = 2.7, 95% CI: 1.3–5.4) at the time of repeat testing. Thus, while their providers were likely to suspect a respiratory infection diagnosis at the time of the initial test (17.5% vs. 14.4% in cases vs. controls; OR = 2.9, 95% CI: 1.1–7.4) by the time of repeat testing, a respiratory infection was even more commonly high on the differential for cases (29.9% vs. 13.9%).

3.3 | Multivariate analysis of risk of conversion

In multivariate analysis, we found that there was no longer a statistically significant association between test conversion and race/ethnicity, exposure status, housing status, or work history (Table 3). Lower SES became associated with a lower odds of conversion (aOR = 0.4, 95% CI: 0.2–0.88). Clinical suspicion for a respiratory infection remained associated with conversion (aOR = 20.9, CI: 3.1–141.2). The lack of pulmonary imaging also remained associated with conversion (aOR = 4.7, 95% CI: 1.0–21.8). A lower burden of comorbidities trended toward significance (aOR = 2.2, 95% CI: 0.9–5.3), though when we removed the cancer center-affiliation variable from the model, a lower burden of comorbidities reached statistical significance (aOR = 3.0, 95% CI: 1.3–7.1) (Supporting Information: Table S1). Our sensitivity analysis removing asymptomatic cases and their matched controls showed similar findings as the primary analysis above (Table 3).

4 | DISCUSSION

In this retrospective, matched case-control study, we examined patient demographic and clinical factors associated with conversion from a negative to a positive NP SARS-CoV2 RT-PCR test result to

TABLE 1 Patient demographics and characteristics at time of initial test among a case-control study, March 2, 2020–July 23, 2020

Characteristic	Case *N* (%)	Control *N* (%)	Total *N* (%)
Age, years			
0–49	35 (36.1)	66 (34.0)	101 (34.7)
50–69	39 (40.2)	83 (42.8)	122 (41.9)
≥70	23 (23.7)	45 (23.2)	68 (23.4)
Sex			
Female	47 (48.5)	82 (42.3)	129 (44.3)
Male	50 (51.5)	112 (57.7)	162 (55.7)
Race/ethnicity			
Non-Latinx White	37 (38.1)	112 (57.7)	149 (51.2)
Latinx	14 (14.4)	15 (7.7)	29 (10.0)
Non-Latinx Black	11 (11.3)	16 (8.2)	27 (9.3)
Asian	8 (8.2)	11 (5.7)	19 (6.5)
Native Alaskan/Native Hawaiian/Native American	0 (0.0)	10 (5.2)	10 (3.4)
Missing	27 (27.8)	30 (15.5)	57 (19.6)
Socioeconomic status			
Higher socioeconomic status	54 (55.7)	93 (47.9)	147 (50.5)
Lower socioeconomic status	42 (43.3)	99 (51.0)	141 (48.5)
Missing	1 (1.0)	2 (1.0)	3 (1.0)
Charlson comorbidity index score			
0	38 (39.2)	34 (17.5)	72 (24.7)
1–2	22 (22.7)	30 (15.5)	52 (17.9)
3+	37 (38.1)	130 (67.0)	167 (57.4)
Comorbidities			
Cardiovascular disease	35 (36.1)	85 (43.8)	120 (41.2)
Coronary artery disease	16 (16.5)	52 (26.8)	68 (23.4)
Chronic obstructive pulmonary disease	13 (13.4)	41 (21.1)	54 (18.6)
Chronic pulmonary disease	39 (40.2)	107 (55.2)	146 (50.2)
Any cancer	12 (12.4)	82 (42.3)	94 (32.3)
Human immunodeficiency virus	4 (4.1)	21 (10.8)	25 (8.6)
Solid organ transplant	5 (5.2)	31 (16.0)	36 (12.4)
Bone marrow transplant	2 (2.1)	18 (9.3)	20 (6.9)
Systemic Lupus Erythematosus	10 (10.3)	41 (21.1)	51 (17.5)
Dementia	7 (7.2)	8 (4.1)	15 (5.2)
Housing Status			
Housed	50 (51.5)	144 (74.2)	194 (66.7)
Skilled nursing/assisted living facility	21 (21.6)	20 (10.3)	41 (14.1)
Homeless	11 (11.3)	22 (11.3)	33 (11.3)
Unknown	15 (15.5)	8 (4.1)	23 (7.9)
Work Status			
Not working on-site	48 (49.5)	124 (63.9)	172 (59.1)

(Continues)

Characteristic	Case *N* (%)	Control *N* (%)	Total *N* (%)
Work on-site	18 (18.6)	17 (8.8)	35 (12.0)
Unknown	31 (32.0)	53 (27.3)	84 (28.9)
Contact with individual with confirmed COVID-19			
Direct contact	15 (15.5)	7 (3.6)	22 (7.6)
Indirect contact	13 (13.4)	5 (2.6)	18 (6.2)
None	7 (7.2)	16 (8.2)	23 (7.9)
Unknown	62 (63.9)	166 (85.6)	228 (78.4)
Contact with individual with suspected COVID-19			
Direct contact	4 (4.1)	0 (0.0)	4 (1.4)
Indirect contact	8 (8.2)	2 (1.0)	10 (3.4)
None	7 (7.2)	19 (9.8)	26 (8.9)
Unknown	78 (80.4)	173 (89.2)	251 (86.3)
Cancer center-affiliation	7 (7.2)	58 (29.9)	65 (22.3)

aid providers prospectively in assessing risk for conversion. Overall, the occurrence of test conversion (deemed as suggestive of clinical false negativity) rate is low (2% in our study). In a multivariate model, initial concern for a respiratory infection and lack of pulmonary imaging was associated with conversion. Persons who were relatively healthy trended toward higher odds of conversion.

Unexpectedly, patients who converted were healthier than controls, both in aggregate with lower CCI scores and when comparing percentages of patients with individual comorbidities (e.g., HIV, transplant, or malignancy). While it was not statistically significant in the first multivariate model, it became significant when the hospital site variable for a specialty cancer center was removed from the model. While cancer center affiliation was not collinear with CCI when tested, it may still be a proxy for greater comorbidities. It is possible that healthier patients have better local control of the virus leading to a lower sensitivity. This finding may also be due to differences in testing criteria. Due to limited testing capacity early in the epidemic, patients with comorbidities may have been tested more frequently than other patient populations, both for diagnosis in high-risk populations or for asymptomatic screenings.[20] Cancer patients are both more likely to have a higher burden of comorbidities than patients without cancer and, since receiving care as part of a "hospital within a hospital," had separate testing criteria (internal guidelines). These factors could have led to more frequent testing of patients with a lower prevalence of SARS-CoV2 positivity, inflating their contribution to our control cohort.[21] We matched controls to cases by test date to account for changes in testing criteria over time, but this may not have accounted for the differences in institutional criteria. Controlling for testing sites should be considered in future studies.

In the multivariate analysis, a lack of pulmonary imaging was associated with an increased odds of conversion. However, among patients who did have imaging, cases were less likely to have abnormal findings. Since some patients had frequent, repeated imaging and sometimes the initial test and repeat test were done in close temporal proximity, we limited review of imaging results to those on the day of the test and excluded imaging done before or after that day. This allowed the reviewers to be consistent across patients and prevented the same imaging findings from being associated with multiple test results. Thus, we advise some caution in interpretation of our findings as related to imaging.

Black or Latinx race/ethnicity, living in a skilled nursing/assisted living facility, and working on-site trended toward an increased odds of conversion in the multivariate model. Many studies have reported on racial/ethnic disparities in incidence and outcomes of COVID-19. Here, we see a trend toward Black or Latinx patients being more likely to convert from negative to positive test results. Delayed diagnosis due to initial negative results, or lack of diagnosis if there is limited access to repeat testing, could be contributing to worse outcomes. Both living in a skilled nursing/assisted living facility and working on site could be associated with increased likelihood of exposure to SARS-CoV2, increasing the pre-test probability of a positive SARS-CoV2 PCR result. With a larger sample size and more complete data, these factors may become statistically significant.

While PCR-based testing is highly specific, sensitivity depends on sample site, suboptimal sampling, timing of testing, or low viral loads.[6] Thus, our hospital system initially relied on repeated testing of admitted patients and physician-to-physician discussions regarding pretest probability of COVID-19 disease before making any decisions on discontinuation of isolation protocols. This resource intensive system was unsustainable as our hospital operations expanded. Therefore, decisions regarding the utility of repeat testing were relegated to individual providers, with some general guidelines. Allowing providers to individually decide to repeat COVID-19 testing increases the risk of premature discontinuation of precautions on some or prolonged work-up for

TABLE 2 Patient clinical characteristics at time of test among a case-control study sensitivity analysis, March 2, 2020–July 23, 2020

	Case (initial test) *N* (%)	Control (initial test) *N* (%)	Case (repeat test) *N* (%)	Control (repeat test) *N* (%)	Total (initial test) *N* (%)	Total (repeat test) *N* (%)
Respiratory symptoms	26 (26.8)	58 (29.9)	38 (39.2)	51 (26.3)	84 (28.9)	89 (30.6)
Upper respiratory tract	11 (11.3)	16 (8.2)	8 (8.2)	13 (6.7)	27 (9.3)	21 (7.2)
Lower respiratory tract	24 (24.7)	56 (28.9)	36 (37.1)	48 (24.7)	80 (27.5)	84 (28.9)
New/worsening cough	14 (14.4)	27 (13.9)	25 (25.8)	21 (10.8)	41 (14.1)	46 (15.8)
New cough at 2nd test	-	-	14 (14.4)	7 (3.6)	-	21 (7.2)
Systemic symptoms	16 (16.5)	34 (17.5)	31 (32.0)	35 (18.0)	50 (17.2)	66 (22.7)
Fever	9 (9.3)	19 (9.8)	25 (25.8)	21 (10.8)	28 (9.6)	46 (15.8)
New fever at 2nd test			19 (19.6)	15 (7.7)	-	34 (11.7)
Other symptoms	33 (34.0)	79 (40.7)	46 (47.4)	70 (36.1)	112 (38.5)	116 (39.9)
Gastrointestinal	3 (3.1)	23 (11.9)	11 (11.3)	23 (11.9)	26 (8.9)	34 (11.7)
Neurologic	12 (12.4)	19 (9.8)	21 (21.6)	15 (7.7)	31 (10.7)	36 (12.4)
Other	8 (8.2)	15 (7.7)	7 (7.2)	10 (5.2)	23 (7.9)	17 (5.8)
Asymptomatic	22 (22.7)	71 (36.6)	16 (16.5)	71 (36.6)	93 (32.0)	87 (29.9)
Unknown	25 (25.8)	13 (6.7)	20 (20.6)	13 (6.7)	38 (13.1)	33 (11.3)
Clinical suspicion						
Respiratory Infection, suspected/confirmed	17 (17.5)	28 (14.4)	29 (29.9)	27 (13.9)	45 (15.5)	56 (19.2)
Other, suspected/confirmed	19 (19.6)	56 (28.9)	15 (15.5)	59 (30.4)	75 (25.8)	74 (25.4)
Asymptomatic screen	12 (12.4)	56 (28.9)	10 (10.3)	47 (24.2)	68 (23.4)	57 (19.6)
Unknown	49 (50.5)	54 (27.8)	43 (44.3)	61 (31.4)	103 (35.4)	104 (35.7)
Pulmonary imaging						
Normal	5 (5.2)	24 (12.4)	1 (1.0)	15 (7.7)	29 (10.0)	16 (5.5)
Abnormal lung imaging	12 (12.4)	46 (23.7)	18 (18.6)	34 (17.5)	58 (19.9)	52 (17.9)
Consolidations on imaging	12 (12.4)	39 (20.1)	18 (18.6)	28 (14.4)	51 (17.5)	46 (15.8)
No imaging	80 (82.5)	124 (63.9)	78 (80.4)	145 (74.7)	204 (70.1)	223 (76.6)
Days of symptoms						
Median (interquartile range)	5 (1–8)	2 (0–8)	4 (2–9)	3 (1–9)	3 (0–8)	3 (1–9)
Missing	6	18	2	27	84	79.0
Days between tests	-	-	7 (4–9)	6 (3.3–8)	-	6 (4–8.5)
Testing location						
Emergency department	27 (27.8)	59 (30.4)	15 (15.5)	27 (13.9)	86 (29.6)	42 (14.4)
Inpatient	18 (18.6)	50 (25.8)	36 (37.1)	105 (54.1)	68 (23.4)	141 (48.5)
Ambulatory	42 (43.3)	76 (39.2)	37 (38.1)	57 (29.4)	118 (40.5)	94 (32.3)
Other	10 (10.3)	9 (4.6)	9 (9.3)	5 (2.6)	19 (6.5)	14 (4.8)

COVID-19 on others. Other screening protocols include scheduled, repeated testing of all admitted patients. This level of testing could also become unsustainable as the prevalence of COVID-19 decreases over time and is, even now, impractical in resource-limited settings. Thus, there is a dire need for evidence based, standardized approaches, and prospective validation of those approaches, to determine which patients should be re-tested for SARS-CoV2.

While our study provides some insights into a possible patient demographic and clinical factor-driven risk stratification

TABLE 3 Logistic regression modeling of patient demographic and clinical characteristics and false positive nasopharyngeal polymerase chain reaction test results among a case-control study, March 2, 2020–July 23, 2020

	Primary analysis				Secondary sensitivity analysis			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age, years								
0–49	Ref	-	Ref	-	Ref	-	Ref	-
50–69	0.9 (0.5–1.6)	0.66	2.0 (0.7–5.6)	0.18	1.1 (0.6–2.1)	0.81	2.0 (0.7–5.6)	0.18
≥70	1.0 (0.5–1.9)	0.89	2.5 (0.7–9.3)	0.18	0.8 (0.4–1.7)	0.53	2.5 (0.7–9.3)	0.18
Sex								
Female	Ref	-	Ref	-	Ref	-	Ref	-
Male	0.8 (0.5–1.3)	0.34	1.1 (0.5–2.3)	0.91	0.9 (0.5–1.6)	0.72	1.1 (0.5–2.3)	0.91
Race/ethnicity								
White	Ref	-	Ref	-	Ref	-	Ref	-
Latinx	2.4 (1.0–5.6)	0.04	2.4 (0.6–9.4)	0.20	2.43 (1.04–5.64)	0.04	2.4 (0.6–9.4)	0.20
Non-Latinx Black	2.1 (0.9–5.0)	0.11	3.8 (0.7–19.8)	0.11	2.06 (0.86–4.96)	0.11	3.8 (0.7–19.8)	0.11
Asian/Native Alaskan/Native Hawaiian/Native American	1.2 (0.5–2.9)	0.73	1.1 (0.3–4.0)	0.89	1.18 (0.47–2.94)	0.73	1.1 (0.3–4.0)	0.89
Socioeconomic status								
Higher socioeconomic status	Ref	-	Ref	-	Ref	-	Ref	-
Lower socioeconomic status	0.7 (0.5–1.2)	0.30	0.4 (0.2–0.9)	0.02	0.77 (0.48–1.26)	0.30	0.4 (0.2–0.9)	0.02
Charlson comorbidity index score								
≥2	Ref	-	Ref	-	Ref	-	Ref	-
0–1	3.7 (2.1–6.4)	<0.01	2.2 (0.9–5.3)	0.10	4.0 (2.1–7.8)	<0.01	2.2 (0.9–5.3)	0.10
Housing status								
Housed	Ref	-	Ref	-	Ref	-	Ref	-
Skilled nursing/assisted living facility	2.9 (1.4–5.9)	<0.01	2.9 (0.8–10.8)	0.11	3.3 (1.4– 7.6)	0.01	2.9 (0.8–10.8)	0.11
Homeless	1.4 (0.6–3.2)	0.39	1.0 (0.3–3.5)	0.96	2.2 (0.9–5.4)	0.08	2.0 (0.3–3.5)	0.96
Unknown	5.1 (2.0–12.8)	<0.01	3.5 (0.8–15.4)	0.10	9.1 (2.9–28.8)	<0.01	3.5 (0.8–15.4)	0.10
Work status								
Not working on-site	Ref	-	Ref	-	Ref	-	Ref	-
Working on-site	2.7 (1.3–5.8)	<0.01	3.1 (0.8–12.0)	0.11	2.7 (1.1–6.5)	0.03	3.1 (0.8–12.0)	0.11
Unknown	1.6 (0.9–2.8)	0.11	1.1 (0.4–2.8)	0.91	1.8 (0.9–3.4)	0.08	1.1 (0.4–2.8)	0.91
Contact with person with confirmed COVID-19								
None	Ref	-	Ref	-	Ref	-	Ref	-
Direct or indirect contact	5.3 (1.7–16.7)	<0.01	3.0 (0.4–19.7)	0.26	6.6 (1.5–28.5)	0.01	3.0 (0.4–19.7)	0.26
Unknown	1.0 (0.4–2.7)	0.98	0.6 (0.1–2.8)	0.55	1.7 (0.5–6.4)	0.04	0.6 (0.1–2.8)	0.55

(Continues)

TABLE 3 (Continued)

	Primary analysis				Secondary sensitivity analysis			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Contact with person with suspected COVID-19								
None	Ref	-	-	-	Ref	-	-	-
Direct or indirect contact	15.6 (2.8–88.2)	<0.01	-	-	3×10^9 (0-INF)	1	-	-
Unknown	1.4 (0.5–3.6)	0.54	-	-	2.6 (0.7–9.4)	0.16	-	-
Respiratory symptoms	1.2 (0.7–2.3)	0.50	-	-	2.3 (1.1–4.9)	0.02	-	-
Upper respiratory tract	2.3 (0.9–5.8)	0.08	0.9 (0.2–4.3)	0.91	2.9 (1.1–7.8)	0.03	0.9 (0.2–4.3)	0.91
Lower respiratory tract	1.1 (0.6–2.2)	0.70	-	-	2.2 (1.0–4.6)	0.05	-	-
New/worsening cough	1.5 (0.6–3.4)	0.38	-	-	2.4 (0.9–6.0)	0.07	-	-
New cough at 2nd test	7.0 (2.4–20.5)	<0.01	-	-	5.4 (1.5–20.3)	0.01	-	-
Systemic	1.2 (0.6–2.5)	0.67	-	-	1.7 (0.8–4.0)	0.19	-	-
Fever	0.9 (0.4–2.3)	0.88	-	-	1.3 (0.5–3.4)	0.62	-	-
New fever	2.7 (1.3–5.4)	<0.01	-	-	2.7 (1.2–5.8)	0.01	-	-
Other symptoms	1.1 (0.6–1.8)	0.84	-	-	2.1 (1.1–4.1)	0.02	-	-
Gastrointestinal	0.3 (0.1–1.1)	0.06	-	-	0.4 (0.1–1.6)	0.21	-	-
Neurologic	1.6 (0.7–3.9)	0.27	-	-	2.6 (1.0–6.9)	0.06	-	-
Other	1.3 (0.5–3.3)	0.54	-	-	1.8 (0.7–4.9)	0.25	-	-
Asymptomatic	0.7 (0.4–1.3)	0.23	-	-	-	-	-	-
Clinical suspicion								
Asymptomatic screen	Ref	-	Ref	-	Ref	-	Ref	-
Respiratory Infection, suspected/confirmed	2.9 (1.1–7.4)	0.03	20.9 (3.1–141.2)	<0.01	17.6 (3.4–92.4)	<0.01	20.9 (3.1–141.2)	0.00
Other	1.6 (0.7–3.5)	0.24	4.9 (1.3–17.9)	0.02	6.6 (1.4–30.4)	0.01	4.8 (1.3–17.9)	0.02
Unknown	4.0 (1.9–8.2)	<0.01	5.0 (1.5–16.5)	<0.01	26.6 (5.6–126.6)	<0.01	5.0 (1.5–16.5)	0.01
Pulmonary imaging								
Normal	Ref	-	Ref	-	Ref	-	Ref	-
Abnormal lung imaging	1.2 (0.4–3.7)	0.72	0.5 (0.1–2.3)	0.38	2.1 (0.6–7.9)	0.27	0.5 (0.1–2.3)	0.38
Consolidations on imaging	1.7 (0.6–5.3)	0.34	-	-	3.2 (0.8–12.3)	0.09	-	-
No imaging	2.9 (1.1–7.8)	0.03	4.7 (1.0–21.8)	0.05	4.1 (1.2–14.1)	0.02	4.7 (1.0–21.8)	0.05
Testing location								
Ambulatory	Ref	-	Ref	-	Ref	-	Ref	-
Emergency department	0.8 (0.5–1.6)	0.60	2.3 (0.7–7.9)	0.19	0.8 (0.4–1.6)	0.56	2.3 (0.7–7.9)	0.19
Inpatient	0.6 (0.3–1.2)	0.14	1.0 (0.3–3.0)	0.98	0.6 (0.3–1.2)	0.15	1.0 (0.3–3.0)	0.98
Other	2.3 (0.8–6.8)	0.12	1.0 (0.2–5.0)	0.95	2.4 (0.7–7.9)	0.14	1.0 (0.2–5.0)	0.95
Cancer center-affiliation	0.2 (0.1–0.5)	<0.01	0.3 (0.1–0.9)	0.04	0.1 (0.0–0.3)	<0.01	0.3 (0.1–1.0)	0.04

approach for false negative test results, it has several limitations. First, it is a retrospective EMR-based study so we were limited by the documentation provided in the individual notes. Documentation of patient characteristics, exposures, and symptoms were inconsistent. A significant percentage of our cohorts had unknown exposures and the majority of patients had no lung imaging on the day of the test. This large amount of missing data is likely contributing to the lack of statistically significant findings.

Second, we included patients who had repeated NP SARS-CoV2 PCR for any indication. Thus, the patient population is heterogenous—the control cohort could be inflated with serial asymptomatic pre-procedure/admission screening, the cases included asymptomatic screenings, those being tested for diagnosis, and those being tested for discontinuation of precautions after transfer from outside facilities for management of COVID-19. Third, this study was conducted before the availability of vaccinations, current prevalent SARS-CoV2 variants, and broad use of antigen testing. With increasing rates of vaccination and infection with variants, we do not know if these findings will remain significant. Finally, we did not control for exposures between test results thus we cannot distinguish between a conversion due to an initial false negative versus new infection. Many studies assessing the clinical sensitivity of the SARS-CoV2 PCR used repeated tests within 7 days.[7,11] While our inclusion criteria allowed for testing up to 14 days apart, most patients had their repeat test within 9 days. Assuming that asymptomatic cases were more likely to be true negatives at the time of their initial test, we conducted a sensitivity analysis by removing them. The interpretation of this analysis is limited since those individuals may have been presymptomatic. Nevertheless, the results of this analysis were consistent with those of our primary analysis.

Despite its limitations, our study does systematically review a patient population undergoing repeated testing in a real-world setting and highlights several counter intuitive risk factors for conversion.

5 | CONCLUSION

This study furthers our understanding of the kinds of patients who may have clinical false positive SARS-CoV2 PCR test results. Interestingly, our findings suggest that a higher index of suspicion for false-negative test results should be maintained for patients presenting with concerns for a respiratory infection and are relatively healthy. We identified additional factors, such as work conditions, residence, and imaging, that should be included in future studies to determine the clinical sensitivity of the SARS-CoV2 RT-PCR. When making guidelines, especially for hospital infection control strategies, a high index of suspicion should be maintained for healthier patients with concern for respiratory infection.

AUTHOR CONTRIBUTIONS

Vidya L. Atluri conceived this study, collected and analyzed data, and drafted the manuscript. Randy M. Stalter and Kristine Lan extracted and analyzed data. Sarah A. McGuffin, Luke Johnson, Bailey Healy, Hailey A. Benesch, and Paula Marsland collected data and edited the manuscript. Paul Pottinger advised on data interpretation and project design. Rena C. Patel conceived and designed the project, advised on data analysis, revised, and edited the manuscript. All authors have reviewed the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data associated with this study are available from the corresponding author upon reasonable request.

ORCID

Vidya L. Atluri https://orcid.org/0000-0002-4830-0569

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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